REMARKS

Claim Amendments

Claims 6-15 have been amended.

Claims 6, 8, 9 and 11 have been amended to delete reference to a fragment comprising an active domain. Claims 7 and 10 have been amended to add an expressed p26 active domain comprising active anti-parallel beta sheets of p26 and an active charged core domain of p26 to the recited group of alpha-crystallin type proteins. Support for this amendment is found in the specification, for example, at page 3, lines 17-20.

Claims 6, 12 and 14 have also been amended to revise the format of the claims to designate the steps with letters followed by parentheses rather than with numbers and periods.

Claim 12 has been amended to clarify that the second protein in the first step (step a) consists essentially of an alpha-crystallin type protein. Claim 13 has been amended to indicate that the alpha-crystallin type protein is alpha-A-crystallin. Support for these amendments is found in the specification, for example, at page 5, lines 13-16.

Claim 14 has been amended to clarify that the first and third steps (steps a and c) refer to "bovine alpha-crystallin protein". Support for this amendment is found in the specification, for example, at page 10, lines 13-15. Claim 14 has also been amended to clarify that the size filtration of step b) is by chromatography. Support for this amendment is found in the specification, for example, at page 10, lines 3-4 and 17-22. Claim 14 has also been amended to clarify that step d) refers to refers to "dialyzing the fraction containing the bovine alpha-crysallin protein into a buffer comprising 50% glycerol and having a pH of approximately 8". Support for this amendment is found in the specification, for example, at page 10, lines 25-28.

Claim 15 has been amended to clarify that the recited filter comprises bovine alpha-crystallin that is coupled to a chromatography resin. Support for this amendment is found in the specification, for example, at page 3, lines 15-16 and page 11, lines 5-7.

No new matter has been added.

Rejection of Claims 6-15 under 35 U.S.C. § 112 for indefiniteness

Claims 6-15 are rejected under 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claimed the subject matter which the applicant regards as the invention.

Claims 6, 8-9 and 11 are rejected for indefiniteness on the grounds that the term "active domain" in the recited phrase "comprising an active domain in bacteria" has been deemed unclear. The claims have been amended to delete the phrase. Accordingly, the rejection is moot.

Claim 14 is rejected for indefiniteness on several grounds. First, the terms "an alpha-crystallin protein" and "the alpha-crystallin protein" are rejected as indefinite on the ground that it is unclear whether it is the bovine alpha-crystallin protein recited in the first line of the claim. Claim 14 has been amended to clarify that the alpha-crystallin protein is "the bovine alpha-crystallin protein". Second, the Examiner stated that the term "size filtering" is unclear because it is unclear as to whether size filtering refers to filtering the sample through filter paper or purifying the protein by gel filtration chromatography. Claim 14 has been amended to clarify that the size filtration is by chromatography. Chromatography is well known in the art and includes, for example, gel filtration chromatography (see page 10, lines 16-25 and page 11, lines 29-30 of the specification) and ion exchange chromatography (see page 12, lines 4-5 of the specification). Third, the Examiner stated that Claim 14, steps c) and d), are indefinite on the ground that they appear to be the same step, and, thus, the order of the steps is ambiguous. Claim 14 has been amended to recite that step d) refers to "dialyzing the fraction containing the bovine alpha-crystallin protein into a buffer comprising 50% glycerol and having a pH of approximately 8". This amendment clarifies the distinction between this step and step c), which relates to neutralizing the fraction containing the bovine alpha-crystallin protein.

Claim 15 is rejected for indefiniteness on the ground that it is unclear whether the term "coupled to" in "coupled to a chromatography resin" refers to the bovine alpha-crystallin protein being covalently conjugated to a resin of the precolumn or a chromatographic pre-column filter being coupled to a chromatographic resin during the purification process as claimed. The Claim has been amended to state that the filter comprises bovine alpha-crystallin protein "that is" coupled to a chromatography resin.

Particularly as amended, the claims are clear and definite. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 6-13 under 35 U.S.C. § 102(e)

The Examiner has rejected Claims 6-13 under 35 U.S.C. § 102(e) as being anticipated by Ambrosius *et al.*, U.S. Patent No. 6,455,279. According to the Examiner, the changes made to 35 U.S.C. § 102(e) by the American Inventors Protection Act of 1999 (AIPA) ("revised § 102(e)") do not apply to the examination of this application because the application being

examined was not filed on or after November 29, 2000 or voluntarily published under 35 U.S.C. § 122(b). Therefore, the Examiner examined the claims under the pre-AIPA version of 35 U.S.C. § 102(e).

The applicants respectfully disagree with this analysis. Revised § 102(e) applies to the examination of all applications, whenever filed. See, *e.g.*, Manual of Patent Examining Procedure § 2136 (8th Ed., Rev. Feb. 2003). The filing date of the application being examined is no longer relevant in determining what version of 35 U.S.C. §102(e) should apply. *Id.* The revised statutory provisions supercede all previous versions of 35 U.S.C. § 102(e). *Id.*

When a potential reference is based on an *international application* filed prior to November 29, 2000, the reference is treated under the pre-AIPLA standard. An international application is defined in the statute as an application filed under the Patent Cooperation Treaty (PCT) (see 35 U.S.C. § 351). When the potential reference is based on an international application, its date for § 102(e) purposes is the date of its compliance with 35 U.S.C. §371 (c)(1), (2) and (4).

Here, however, although the Ambrosius patent claims the benefit of priority of European application EP 99114811, it does not claim the benefit of an international application filed under the PCT. Therefore, its effective date as a potential prior art reference is its U.S. filing date, July 19, 2000) (see revised § 102(e)).

The examined application claims the benefit of priority of provisional application 60/201,407, filed May 3, 2000, two months before the Ambrosius patent. Therefore, the Ambrosius patent is unavailable as a prior art reference.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 14 under 35 U.S.C. § 103(a)

Claim 14 has been rejected as being obvious over Stevens A *et al., Curr. Eye. Res., 6*:739-740 (1987) taken with Reddy, G.B. *et al., J. Biol. Chem., 275*:4565-4570 (2000).

According to the Examiner, Stevens teaches a method for purifying bovine alpha-crystallin protein using gel filtration chromatography, comprising dissolving the alpha crystallin protein in a glycine solution (pH ~2.5). The Examiner stated that, after the gel filtration step, neutralizing the acidic pH to pH 8 as taught by Reddy would have been apparent to the skilled artisan to store the purified crystallin protein for further use.

Claim 14 has been amended to clarify that the neutralization step and the dialysis step are distinct from each other. After the fraction containing the bovine alpha-crystallin protein is

neutralized (step c), it is then dialyzed into a buffer comprising 50% glycerol and having a pH of approximately 8 (step d). This dialysis step is necessary because the elastase inhibition activity is strongly affected by ionic strength (*see, e.g.,* lines 28-29 of page 10 of the specification). The high glycerol in the buffer can concentrate the purified protein significantly (*see, e.g.,* lines 7-9 of page 10 of the specification, regarding the purification of p26).

Stevens teaches isolation of alpha-crystallin subunits. It does not teach or suggest the advantageous glycerol dialysis step recited in the Claim. Stevens does not even mention dialysis, or provide a motivation to alter ionic strength. Nor does Stevens teach or suggest the use of 50% glycerol to increase purified protein concentration. Reddy does not compensate for the insufficiencies of Stevens. Reddy discloses a method for purifying human alphaA- and alphaB crystallin. Reddy does not teach or suggest the use of 50% glycerol to increase purified protein concentration. Thus, Reddy does not teach the missing step of Stevens, and the combined teachings of Stevens and Reddy do not teach or suggest all of the elements of Claim 14.

Therefore, one of skill in the art would not have been motivated to combine the teachings of Stevens with the teachings of Reddy to practice the advantageous glycerol dialysis step claimed in Claim 14.

Thus, particularly as amended, Claim 14 is not obvious. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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